A Unified Concept of Health and Disease*

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In the article which follows, Dr. George L. Engel, Professor of Psychiatry and Associate Professor of Medicine at The University of Rochester School of Medicine and Dentistry, discusses some concepts of health and disease and considers the practical question of how we know that someone is sick. We hope the ideas presented will interest our medical electronic readers.

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IN 1951, at the dedication of the Insitute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hosiptal, I first attempted to formulate a unified concept of health and disease.[1] The present paper is an extension and to some extent a reformulation of that work.

I. GENERAL PRINCIPLES

A. Unitary Concept of Health and Disease vs Unit Causes

Medicine is concerned in the broadest sense with the problems of health and disease and, more specifically, with the mechanisms and the processes whereby health is maintained or disease develops. Health and disease are relative concepts which do not easily lend themselves to simple definition. Romano has proposed the following formulation: "Health and disease are not static entities but are phases of life, dependent at any time on the balance maintained by devices, genically and experientially determined, intent on fulfilling needs and adapting to and mastering stresses as they may arise within the organism or from without. Health, in a positive sense, consists in the capacity of the organism to maintain a balance in which it may be reasonably free of undue pain, discomfort, disability or limitation of action, including social capacity."[2] Disease corresponds to failures or disturbances in the growth, development, functions, and adjustments of the organism as a whole or of any of its systems. Clearly, such a definition is too broad to be of practical value. However, it is useful as a starting point. It may be contrasted, for example, to the cellular concept of disease, which by focusing primarily on changes within the cell as the basic component of disease actually restricts attention to only one aspect of disease, and one which is not necessarily present. It tries to get away from the implicit assumption that disease is a thing in itself, unrelated to the patient—a concept of antiquity which repeatedly reasserts itself even in our language, as when we say that a patient has a disease or that we treat a disease.[3] It does not confine our attention to any single system of organization of the body, permiting us to conceptualize disturbances at any level of organization—biochemical, cellular, organ, psychological, interpersonal, or social—and to consider their interrelationships. Further, it permits the application of a multi-factor concept of etiology.

An important aspect of many concepts of disease has been that unconscious psychological factors continually operate in the minds of the observers to distort reality. The most important of these is the tendency to ascribe disease to a "bad" influence, usually something external which gets into the body and then causes disease. This theme characterizes primitive and prescientific views of disease. To be able to think of disease as an entity, separate from man and caused by an identifiable substance, apparently has great appeal to the human mind. Patients prefer to blame their illness on something they "caught" or ate, or that happened to them, and to think of disease as something apart. Physicians also find such ways of thinking attractive, particularly if they can see the "cause" of the disease as something which they can attack and destroy. Because such ideas have strong unconscious appeal, new scientific contributions are repeatedly reformulated in terms of the bad agent or the single cause. The germ theory, for example, easily lent itself to such distortion since it included the concept of invisible, omnipresent agents which produce disease. The failure of the cellular concept of disease to explain more than some mechanisms of disease is now leading to the concept of the biochemical defect as the underlying cause of disease. Again, the search is for the single defect, an abnormal en-

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[1] G. L. Engel, "Heomeostasis, behavioral adjustment; and the concept of health and disease," in "Mid-Century Psychiatry," R. Grinker, Ed., Charles C Thomas, Springfield, Ill., pp. 35-59; 1953.

[2] J. Romano, "Basic orientation and education of the medical student," *J. Am. Med. Assoc.*, vol. 143, p. 409; 1950.

[3] I. Veith, "Psychiatric nosology: from Hippocrates to Kraepelin," *Am. J. Psych.*, vol. 114, p. 385; 1957.

zyme or biochemical system, as the cause of each disease. Regardless of whether disease is equated with an anatomical, a physiological, or a biochemical lesion the psychic distortion in the observer generally involves the idea of the discrete "thing" inside the body, an entity having an existence of its own, apart from the patient, who is the helpless victim.

Another variation on this theme is the mechanistic concept, which sees the body as a machine and disease as a condition due to a defective part. A misbehaving organ or system again fulfills the idea of the disease as a thing apart. Even the various "stress" theories currently popular are not immune to this unconscious psychic influence, "stress" being viewed as a "bad" force to which the person falls victim. The bad influence may be inside as, for example, the "bad" emotions, such as rage, fear, envy, greed, or disgust. Characteristic of all these concepts of disease is the emphasis on or search for the single factor which can qualify for the role of "bad" and which is then to be attacked.

B. *Nosology as a Circumscribing Factor*

Another difficulty in formulating a general concept of disease has been the inhibiting influence of nosology. Necessary and valuable as it is to be able to classify and categorize the phenomena of disease, the application of a name may also over emphasize one aspect at the expense of others or imply a degree of certainty to our knowledge which is not actually justified. Names for diseases often have originated from the more obvious, not the most important characteristics of the condition. Thus, pernicious anemia is not just a disease of the blood and it is no longer pernicious. The names used generally reflect the state of knowledge of the condition at the time it was identified, and although names are rarely changed our understanding of the processes involved are constantly changing.

What do the diagnostic names tell us? Diagnostic labels are ways of indicating categories of information about our patient. A diagnostic label rarely, if ever, fully defines the illness. Rather, it has statistical and predictive value. Thus, if we are told that a man has tuberculosis, we assume that he harbors the tubercle bacillus and *we can predict the probability of his having certain signs and symptoms.* On the other hand, we cannot assume that he has any or all of these signs and symptoms nor can we assume that he does not have other signs and symptoms which are not statistically related to the diagnostic term "tuberculosis." Nor can we even assume that if the patient does have the predicted signs and symptoms, all or any of them are necessarily related to the tuberculosis. In practice, of course, we proceed from the other end. We listen to the patient's story and we subject him to various types of examinations and then we attempt to categorize the areas of the patient's illness in which we feel we have understanding and we represent these by the appropriate diagnostic terms. In the course of study of a patient a great deal of other information is revealed, some of which may and some of which may not contribute to the decision about diagnostic categories, but much of which does not lend itself to any such categorization. Yet this unclassifiable information is also essential for the physicians understanding of how, and perhaps also of why the patient is sick. Thus, while the physician's obligation is to establish the clinical diagnosis, this is not an end in itself but is the physician's way of indicating those aspects of the patient's illness which he knows and is able to identify as established by experience and convention. Such diagnostic terms, however, do not include other important aspects or other important knowledge about the patient, nor do they include other diagnostic categories or even other phenomena which have not yet been categorized in diagnostic terms.

C. *A Look at Tuberculosis as an Example*

Having considered some of the factors that subtly influence the way physicians view disease, we may now examine the application of the broad concept of disease. This may be accomplished by a hypothetical example, such as might be postulated in the various possible relationships between man and the tubercle bacillus. Customarily we think of the tubercle bacillus, the bad agent, as causing tuberculosis. But it has the potentiality of producing disease in man in a number of ways:

a) It is a parasite that can compete with certain tissues of the body for nutriment and it elaborates certain materials which are damaging to cellular systems. It may thereby produce tissue changes and a response of the host which the pathologist identifies as "tuberculosis."

b) The concept of tuberculosis as a known contagious disease may have certain symbolic meanings for an individual and may mobilize or be utilized for certain phobic or delusional processes.

c) The presence of tuberculosis in one individual may alter his relationships with another person in such a way that the latter is frustrated or that certain needs remain unfulfilled. Failure to adjust successfully to this new situation may be expressed as illness in the second person.

Whether or not disease will develop in any of these situations depends upon a number of circumstances. Clearly, only in the first category is the tubercle bacillus directly involved and is the diagnostic category "tuberculosis" justified. But everything that develops in this first category will not be understandable exclusively in terms of the relationship between the tubercle bacillus and the body of the host. Under any of these circumstances, whether or not disease develops will depend upon a variety of factors. Various theoretical possibilities may be summarized as follows:

1) The organisms may be of low virulence or of insufficient number. Although inhaled or ingested, they do not have the capacity to penetrate the cellular barrier and gain access to the interior of the body. They are dealt with as inert foreign bodies. No disturbance of existing defenses occurs; no mobilization of new defenses of sufficient magnitude to alter the bodily state is necessary; there is no disease.

2) The organisms are virulent but the resistance of the host is adequate to circumscribe and destroy the organisms locally. This may involve a local tissue change, including the formation of a Ghon tubercle, but there may be no change in the total body economy that is subjectively experienced by the person in whom this process is taking place. From the individual's point of view, no illness was experienced. However, an X-ray examination or a tuberculin test may reveal to the physician that this process of adaptation had taken place. This may constitute one of many successful adaptations experienced by this individual but it does not constitute a disease. As a result of this adaptation the individual now has a different and usually an enhanced capacity to deal with further exposures to the same organism.

3) In contrast to the example just cited, the primary lesion of tuberculosis may be apparent to the individual, as when it develops in the skin as the result of a penetrating injury by a contaminated instrument. For some individuals, the development of a painless skin nodule or ulcer might pass unnoticed or might arouse only slight curiosity. Other individuals might experience considerable concern and may feel it necessary to consult a doctor. A medical student or a pathologist, knowing that he incurred this injury in the course of autopsying a cadaver with tuberculosis, would most likely experience considerable concern and may have a variety of symptoms, perhaps some simulating tuberculosis. But such clinical manifestations would be largely of a psychological nature and would have no direct relationship to the activity of the tubercle bacillus *per se*. Even though this local infection healed spontaneously with minimal tissue change, the patient's total illness experience would be quite different from that when the primary infection was in the lung and ran its course silently, without ever becoming known to the person.

4) The classical situation is that in which virulent organisms gain access to the lung and overcome local defenses. This may occur on first exposure or when a change takes place in the resistence to organisms already present. The capacity of the host to resist the virulent organisms either was inadequate to begin with or it changed. A series of events are set in motion, some of which are experienced by the patient as symptoms, some of which are manifest to the physician-observer as signs, and some of which are detectable only by special techniques of examination. In aggregate, these represent the various ways in which the patient responds to the virulent organism, as well as to the situation of reacting to the virulent organism. The processes are taking place simultaneously at many different levels of organization, as follows:

a) There is a local tissue process which results from the destructive effects of the tubercle bacilli on the lung tissue and from the various attempts of the body to overcome and confine the invaders locally, to protect tissues from further damage, and to restore damaged tissue.

b) General biochemical and physiological processes are set in motion as part of the "behind the line" activity to support these local processes. Some of these are reflected in such manifestations as increased metabolism, fever, sweating, loss of weight, altered respiration, changes in circulating white cells, plasma proteins, and so forth.

c) As various systems of the body are brought into action to cope with the local process, this eventually influences total behavior. Central neuro-humoral systems will already have been activated and with these must eventually come an impact on systems of internal perception of the mental apparatus indicating the change in the bodily status. This changing status may first be perceived consciously as an affect, a general sense of malaise, fatigue, restlessness, uneasiness, vague anxiety, decreased interest in activity, etc., and only later may more specific symptoms, as cough, sputum, etc., be noted. The former manifestations are nonspecific. They represent the activation of the signal functions of ego, affects indicating a change from the pre-existing dynamic steady state. Such manifestations are highly individual and the form which they assume is determined by the past psychological experience of the individual. But they indicate only that the patient is sick, nothing more. The more specific symptoms—cough, fever, sputum, etc.—are more indicative of the local pathological changes and provide the clues for the diagnosis of the specific disorder. In each case the affective responses to the perception of the pathological changes going on in the patient's body will make connection with past experiences associated with similar effects and not necessarily with past experiences associated with similar pathological processes. The psychic defenses that are mobilized to deal with these unpleasant feelings will also be an expression of the person's usual way of dealing with such feelings and they will be highly individual. Thus one person may focus quickly on a specific manifestation, such as cough, while another may minimize such specific manifestations and present mainly the more general phenomena. Another person may need to deny weakness or disability because of his psychological background and hence may acknowledge no symptoms until the tissue changes are far advanced. Still another person may respond to the specific symptoms with overwhelming anxiety or depression.

d) Social and cultural factors will also influence how the disorder is experienced by the patient, by the environment, and by the physician. Such factors may determine what symptom the patient selects to present to his family or to his physician, and what symptom he may elect to minimize or conceal.

5) Once having had active tuberculosis, the degree of recovery may not be uniform in all systems involved.

Among some individuals there may be complete healing of the local process; they may be left with no demonstrable difficulty in respect to pulmonary or other functions and they may be able to return successfully to their previous level of adjustment, occupation, etc., and to function effectively thereafter. Yet in many respects they are different by virtue of having experienced this illness. Among other patients the tubercle bacillus may be eliminated as an active pathogenic agent, but there may remain varying degrees of irreversible damage to the lung or other structures resulting in some decrement in functional ability of the individual. This may require a psychological and social adjustment which he may or may not succeed in achieving. Still other patients may have complete healing of the local tubercular process and no residual anatomical defect and yet may continue to have a variety of describing symptoms. Some patients may be improving or even be symptom-free until the time of discharge from the hospital, only then to develop new symptoms. In the last two examples the pathological process at the cellular and organ level has been successfully resolved but a disturbance in psychological adjustment remains. This is no less an illness than was the tuberculosis and may, indeed, prove to be even more incapacitating to this individual.

6) The occurrence of active tuberculosis in one member of the family may contribute to the development of illness in other members of the family. The disruption in a family unit, the loss of a psychic object (husband, wife, mother, father, child), the increased burdens or the deprivations imposed upon the other members of the family, the mobilization of ambivalent feelings toward the sick person—all of these may in the susceptible family member eventuate in illness. The nature of the illness so precipitated cannot be predicted. One individual may decompensate in a largely psychological fashion and manifest neurotic, psychotic, or behavioral disturbances. Another individual, decompensating with feelings of helplessness or hopelessness in relation to what he is experiencing, may prove susceptible to a preexisting or an intercurrent process which is eventually manifested somatically, such as diabetes, an infection, cardiac decompensation, etc.[4] A great number of factors will determine whether a person falls ill and if so, when and in what way. In these examples the tubercle bacillus and tuberculosis are only indirectly involved. The stress is primarily psychological and the immediate response is psychological. Whether there will also be decompensation involving somatic symptoms is determined by other factors, some somatic and some biological.

7) The concept of the tubercle bacillus as a dangerous agent, or of tuberculosis as an internally destructive process may become the content of a phobic or delusional system. In this type of situation the tubercle bacillus and/or tuberculosis are symbolic expressions of some fearful feeling or idea of the patient. As such they are generally substitutes for some unacceptable impulse. Thus, the delusion of having tuberculosis and being destroyed by it may represent the patient's way of dealing with his own unacceptable or sexual impulses, or may represent his way of dealing with an ambivalent object which he experiences as actually inside him and destroying him. The fear of contamination, perhaps taking the form of contamination by the tubercle bacillus, again may represent the projection to the outside of the patient's own feared or unacceptable impulses.

These seven examples are intended to illustrate in broad terms the many levels of behavior and response characteristic of any disease process. Whether or not the tubercle bacillus is actively involved, the response of the host takes place simultaneously at many different levels. Not all of these responses are adaptive; particularly, they are not necessarily adaptive in respect to the interaction with the tubercle bacillus.

II. DISEASE AS A NATURAL PHENOMENON

Obviously there is no sharp dividing line between health and disease, nor are all parameters of the adaptive process necessarily equivalently involved. A person may satisfy all the criteria of health at any point in time simply because the adaptive capacity of a defective system, be it biochemical, physiological, or psychological, has not been exceeded. This may be a matter of fortunate circumstances or of the infrequency of the factors which would put the system under strain. Or it may be a matter of time; eventually the system will break down under the impact of accumulated and repeated small stresses. This principle is best illustrated in relation to some genically determined defects which may only eventuate in manifest disease after a lapse of time or under particular circumstances—or perhaps never at all. Or after a disease experience, a limitation in the adaptive capacity of an organ or system may result, but the person may be healthy in all other respects unless, or until, he strains the capacity of that organ or system beyond its limits of adjustment. A mitral heart valve damaged in the course of rheumatic fever may impose a limitation on the range of possible circulatory adjustment, but this may be inapparent for many years, during which the person "enjoys good health." The physician's knowledge of the presence of such a potential limitation and the likelihood of eventual breakdown does not alter the fact of relatively good health over a certain span of time, especially when we realize how many persons must carry potential limitations completely unknown to themselves or to physicians. But even when there is gross and manifest disability, we must recognize the relative integrity of other systems or modes of function, permitting us to speak quite correctly of the "more healthy" parts of the body or the person.

Such considerations naturally raise the practical question of *how do we know that someone is sick*. We need not concern ourselves with the deviations in structure, performance, or behavior that are so gross as to be obvious even to an untrained person. Rather, we need to examine some *generalizations that will enable us to identify the state of*

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[4] A. H. Schmale, Jr., "Relationship of separation and depression to Disease," *Psychomat. Med.*, vol. 20, p. 260; 1958.

disease regardless of its severity, etiology, or the particular systems involved. We must also be able to identify the potential for breakdown in the apparently healthy individual. As a starting point, we can say that *the presence of a complaint must be regarded as presumptive evidence of disease.* It indicates that there is a disturbance in the dynamic steady state, and that this disturbance is now being reflected consciously as something unpleasant. The complaint itself does not necessarily give any information as to the severity or nature of the process. It may be addressed to a physician or member of an allied profession, a member of the family, a friend, or it may be kept to himself. This is a *symptom*—something subjectively and privately experienced which may or may not be communicated to someone else in the form of a complaint. It might involve something also apparent to an outside observer, such as a swelling, or peculiar behavior, in which case it is also a *sign.* Whether or not a complaint is communicated depends upon a great number of factors, some personal, some social, and some cultural.

On the other hand, the absence of a complaint (a symptom) cannot be equated with the absence of disease. Significant disturbances involving physical as well as psychological processes may be kept out of consciousness so successfully that patients may show major defects or changes in parts of their body, in their physical functioning, in their behavior, or in their thinking processes and yet may deny the fact that any change has taken place. An observer, lay or professional, may immediately recognize that the person is ill. This situation, however, differs from that where some technique of examination, physical, psychological, or laboratory, reveals to the physician a defect which is at the moment compensated for, or is simply not involved in the person's current function. Such conditions fall in the borderland between health and disease, involving as they do relative or potential disability, but adequate function under most circumstances.

This perspective is, of course, much broader than the conventional one. It is customary in medicine, when attempting to establish whether a person is ill or not, to place the greatest emphasis on that which can be determined objectively; *i.e.,* by the physician, rather than the patient, often preferably by some impersonal instrument, such as a laboratory procedure. Regardless of the nature and the severity of a patient's complaint, the failure to discover an abnormality on physical or laboratory examination means to many physicians that there is "nothing wrong." In common slang, the patient has "no pathology," and it carries the double implication that he is not sick and often also that he is not worthy of help or that he is "fooling" the physician. If the patient responds to the simple reassurance, "There is nothing wrong" (as some patients do), this may be regarded simply as a demonstration that there really was nothing wrong rather than that the patient had been experiencing some kind of disturbance which was alleviated by this type of reassurance. Another aspect of this attitude is that when some type of somatic or physiological abnormality is demonstrated, the correction of this abnormality may be equated with cure, regardless of the patient's subjective experience. The extreme of this is the not-so-humorous statement, "The operation was a success but the patient died."

Some may argue that this broadens the concept of disease so much as to render it virtually useless. Experience refutes this argument. The traditional attitude toward disease tends in practice to restrict what is categorized as disease to what can be understood or recognized by the physician and/or what he notes can be helped by his intervention. *This attitude has plagued medicine throughout its history and still stands in the way of the physician's full appreciation of disease as a natural phenomenon.* Disease cannot be defined on the basis of the *function* of physicians, which is a social and institutional phenomenon. The scientific attitude requires that a clear distinction be made between the study and understanding of disease as a natural phenomenon and the categorization of disease in terms of the function and role of the physician in a society. Only the first is relevant to a scientific concept of disease. The latter changes with time and circumstance.

Viewing disease from such a naturalistic rather than an institutional perspective means that many processes may be thought of in terms of disease which are not currently so regarded. For example, the experience of grief which ordinarily follows the loss of a loved person, a valued possession, or an ideal, fulfills all the requirements of a disease process as we have defined it. The usual arguments to dispute such a point of view are as follows: First, even though everyone recognizes the magnitude of suffering and disability accompanying grief, it is regarded as "natural" and expected, meaning that anyone who suffers a loss would be expected to experience grief. But it is also "natural" for an orderly sequence of events to take place in the tissues following a penetrating wound or the ingestion of viable typhoid bacilli. As is also true of the sequellae of a wound or of ingestion of typhoid bacilli, not everyone experiences grief following a loss and, among those who do experience grief, not all experience it in exactly the same way. A second argument is that grief is a self-limited process which one can expect to get over without help. Even when this is so (and it is not always), the same may be said of many situations which are commonly categorized as within the domain of disease. Wounds also may heal and infections run their course without any intervention by a physician, but this does not make such processes any less disease experiences. A third argument is that a person suffering a loss is not expected to consult a physician for the diagnosis and treatment of the ensuing grief. If the physician is to consider him as a patient, convention dictates that the patient present with a "legitimate" complaint, *e.g.,* a physical symptom. Indeed, this is what usually happens. The grieving patient brings a physical complaint and the physician may never even learn of the bereavement. If he does, he may regard it as "natural" and irrelevant, or "noncontributory," ignoring the fact that the basis for this judgment was neither examined nor established. Many other types of examples could be given. What I wish to emphasize is that many phenomena of everyday life which are considered natural are not customarily regarded in terms of disease, even though they involve processes which basically do not differ from those which are involved in disease. The term "pathological" is a relative one, and one which is set by convention—medical, scientific, and even social. And such conventions change so that what may be considered as illness or disease at one time, or by one person, may not have been so considered at another time, or by another person. Epilepsy, drug addiction, and psychosis are examples of disease processes which have been variously regarded at different times and by different people. That such conventions have use does not bear on the validity of this point of view.

III. ETIOLOGICAL CONSIDERATIONS: THE NECESSARY AND SUFFICIENT CONDITIONS

We now turn our attention to the factors concerned in the genesis of disease, the etiological factors. *We define etiological factors as factors which either place a burden on or limit the capacity of systems concerned with growth, development, or adaptation, or as factors which, by virtue of their physical or chemical properties, have the capacity to damage cells or parts of the body.* They may operate through the impact of something added to or impinging on the system as well as by virtue of a deficiency, as when something required is inadequate or unavailable. They may originate within the organism as well as in the environment. It should be clear that no etiological factor can be considered in the abstract, but only in relation to the system or systems upon which it is operating. Furthermore, factors which have etiological significance in respect to a disease process at one time or under one circumstance may at another time or under other circumstances not have such implications, and vice versa. *One never deals with a single etiological factor in the genesis of a disease state,* although one factor may be more important than others or there may be practical advantages in paying more attention to one factor than to others. To quote Shimkin, "There are few, if any, simple or single causes in biology; there are instead complex situations and environments in which the probability of certain events is increased."[5] The scientific approach to disease assumes multiple factors, some more proximate, some more distant in time; some more specific, some more general in their effects; some necessary, but not in themselves sufficient to bring about the condition of disease. We may qualify the role of any factor by such adjectives as "precipitating," "conditioning," "predisposing," "permissive," "specific," or by indicating its mode of action; *viz.*, genic, biochemical, physiological, psychological, social, etc. Postdictively we seek to identify the conditions necessary and sufficient to bring about a particular constellation of signs and symptoms. As physicians we intervene where we can to aid in the restoration of a state of health. As medical scientists we study these factors in terms of their qualifications as necessary and/or sufficient conditions, and attempt to predict the probability of occurrence of a particular constellation of manifestations characterizing a disease state. Again, as therapists we attempt to prevent the occurrence of the disease state by interfering with the operation of one or more factors before the necessary *and* sufficient conditions have been achieved. The scientific attitude can permit no restrictions as to the category of natural phenomena investigated.

Let us now examine more closely some categories of etiological factors. The strictures of speech prevent us from discussing more than one at a time but this does not obviate the fact that in nature many processes will be operating simultaneously.

A. *Factors Which Determine the Capacity of the Organism to Grow, Survive, and to Adapt*

1) Genic Factors: These are factors which are to be understood exclusively in biochemical terms, referring to the chemical composition of the body as determined by genic inheritance. They include factors underlying the individual chemical characteristics of the cells of each person and as such contribute to the basic chemical structure underlying the capacity for growth and development of every cell and system. We may presume that a normal distribution curve will describe the ranges and the capacities of each biochemical system in the population and hence, the limit of functional or structural potential of the system for each individual. This refers to what we may speak of as the "biochemical universals," namely those systems which occur in all humans and which are generally regarded as "normal." This perspective emphasizes the genically determined variance within the normal biochemical systems of the body. This variance will describe one of the categories of factors concerned both with the potential for growth and development as well as the capacity to adjust to changes imposed from without or from within. It will be a remote factor, one in a chain of events which may prove critical in a breakdown at some later date. Its influence may range all the way from the activity of enzyme systems to what people look like.

In addition, genic factors also play a role in the transmission of abnormal or defective biochemical systems responsible for the variety of so-called inborn errors of metabolism. These may include factors which are incompatible with fetal survival, factors which produce or are responsible for major developmental defects, and factors which may become manifest only under particular circumstances and at particular times in development. Among some of the better studied examples are such conditions as sickle cell trait, glycogen storage disease, hereditary phenyl pyruvate oligophrenia, congenital glactosemia, gout, porphyria, etc.[6,7] These relatively rare conditions lend themselves to study because the defect represents such a striking deviation from the normal. Yet it seems likely that many other more common conditions such as diabetes, pernicious anemia, peptic ulcer or coeliac disease, for example, will prove to involve similar factors.[8] Whether or not genically carried inborn errors become manifest in the form of a recognizable disease state depends on nonspecific as well as highly specific factors having to do with the particular defect as well as with developmental processes. The intestinal malabsorption of coeliac syndrome apparently requires the presence of a wheat protein in the diet. This is an example of a condition in which substances normal to the diet are harmful to those individuals who carry the enzyme defect.

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[5] M. B. Shimkin, "Hormones and neoplasia," in "Cancer," vol. I, R. E. Raven, Ed., Butterworth & Company, London, Eng., p. 161; 1952.

2) Developmental Factors (other than genic): These include all the factors, from conception on, which influence developmental and adaptational capacities favorably or unfavorably. This developmental perspective takes into account all the ways in which the organism and its component parts in the course of development "learn" to secure needs and to adjust to stress, including those provoked by deprivation or insufficiencies. We postulate that within the framework provided by the genically determined structure, the nature and variety of experiences during life, including prenatal, will determine the specific ways of development, the particular variety of techniques utilized to relate effectively to the external environment, and the particular varieties of defense, ranging from cellular to psychosocial. The concept of object relations is important here. We include in the concept of objects all varieties of external things or processes which must sometime in life be taken in physically or psychically and become part of the organism, ranging from molecules to percepts of persons, ideals, etc. At the level of cellular function we note the capacity of the cell to "recognize" and select what it needs for its own development and to reject or actually defend itself against damaging molecules. After a particular microorganism or foreign protein has gained access to the body, the body may thereafter be permanently changed so that the cells "recognize" this foreign substance and react differently to it. Some such changes may be permanent (*e.g.*, immunity), while others may develop slowly and last only as long as the substance is present, during which time it becomes essential.

At the level of the organism as a whole we note the variety of influences, notably persons and situations, which the individual comes to experience as providing something necessary for continued effective functioning, and the absence of which may be experienced as a loss requiring some type of adjustment—grief being the most typical response. Here we would only emphasize the highly individual nature of such object relationship capacities and in what way they help to determine what constitutes the strengths and weaknesses of the inidvidual—what he comes to need from his environment in order to remain in comfort and to function effectively.

Thus, a host of processes occurring at a cellular or biochemical level early in life, sometimes only at a particular time, may be critical in determining the capacity of a person to develop certain pathological changes later in life, and the time at which these occur may be critical in determining whether there will be a later effect and if so, what this effect will be. This principle also holds in respect to the development of the mental apparatus where the character and effectiveness of ego mechanisms in maintaining balance are greatly influenced by the nature of early life experience, especially those concerned with object relations. Thus, at any latter point in time, what constitutes a stress to any individual will be determined to a large degree by the nature of his past experience (as well as by the character of his genic endowment). This will apply to the nature of the response to microorganisms as well as to the loss of a love object. By virtue of what has gone before, the person may be more or less able to cope with ingested typhoid bacilli and more or less able to tolerate the death of his mother.

B. *Factors Which Strain Current Capacities of an Organism*

Having emphasized the influence of past experience on determining both the capacities for adjustment and the specific vulnerabilities and tolerances, we can now consider the varieties of processes which can put such capacities under strain. Because such factors are usually more obvious and certainly more proximate, they are often inaccurately designated as "the cause" of the disease process. We divide such factors into a number of categories.

1) Factors Which Injure by Virtue of Their Physical and/or Chemical Properties: These include all the varieties of physical and chemical noxa which may impinge upon man from the external environment; *e.g.*, mechanical forces, poisons, heat, cold, radiation, electricity, etc., as well as substances which are formed or forces which may develop within the body which injure by virtue of inappropriate quantity or location; *e.g.*, excess insulin or action of gastric juice on the esophagus. Such internal factors are almost always secondary to the other factors, but nonetheless may bring about effects (signs and symptoms) which are specific and not necessarily related to the predisposing factors.

The external noxa come the closest to constituting absolute causes in the sense that beyond a certain degree many will be damaging or lethal to everyone. Even here, however, there are important predisposing considerations. Persons differ in respect to the magnitude of a blow, the dose of a poison, or the amount of sunlight that can be tolerated. Furthermore, many psychological and/or social factors may be critical in determining the circumstances of the exposure

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[6] H. M. Kalckar, "Some considerations regarding biochemical genetics in man," *Perspectives in Biol. and Med.*, vol. 1, p. 3; 1957.

[7] L. H. Snyder, "Fifty years of medical genetics," *Science*, vol. 129, p. 1; 1959.

[8] I. A. Mirsky, "Physiologic, psychologic, and social determinants in the etiology of duodenal ulcer," *Am. J. Digest. Diseases*, vol. 3, p. 285; 1958.

in the first place, such as those which are involved in suicide, accident proneness, impulsivity, industrial exposure, pure coincidence and so on. Some of these agents (for example, carcinogenic substances or radiation) do not necessarily produce their effects immediately or in all who are exposed. In general, the longer the time lapse between an exposure to a noxious agent and the development of pathological tissue changes, the more complex and multiple the other conditions necessary for such pathological developments are likely to be. Some molecular substances achieve a noxious quality only by virtue of the host's capacity or tendency at certain times and under certain conditions to develop a specific type of altered response, the allergic reaction.

2) Physical Factors Which Lead to Injury When Insufficient or Unavailable: In this group we restrict ourselves to the essential chemical elements (oxygen, water, electrolytes, nutriments, vitamins, etc.) which the organism must obtain from the environment (deficiency states), as well as essential substances formed in the body, *e.g.*, hormones (insufficiency states). Again, we must keep in mind the predisposing conditions which determine why the deficiency or insufficiency occurred in the first place, as well as the magnitude and character of the resulting reaction. Here again the less immediately or less consistently developing reactions either involve less critical substances or require the operation of multiple predisposing or intermediary processes before the conditions necessary and sufficient for manifest disorder are reached. We can contrast the relatively narrow range of resistance to oxygen lack and the more variable response to lack of a single nutritional element, or the pronounced response to insulin insufficiency as compared to the minor effects, if any, of gastric hydrochloric acid insufficiency.

3) Microorganisms and Parasites: These deserve a special category in the etiology of disease because they involve the interrelations between two or more living systems. In the case of each agent there are highly specific as well as nonspecific factors which determine a) whether it gains entry to the body; b) whether it exists there in a harmless parasitic or in a helpful or neutral symbiotic relationship, or whether it damages or destroys its host; c) in what particular locus, *i.e.*, cell, tissue, organ, or body fluid, it can live. There are some microorganisms to which humans are almost universally susceptible on first exposure (*e.g.*, the viruses of measles and small pox) so that the most significant factor determining susceptibility to infection (though not capacity for survival) may be survival from previous exposure and the acquisition of immunity. Other microorganisms may be capable of infecting only a small proportion of people, and others may at some point in the life of the host or of the microorganism change from a harmless guest to a destructive agent. Some consequences of infection with microorganisms may be indirect and dependent on the characteristics and condition of the host, so that only certain individuals at certain times may so react; *e.g.*, the relation between hemolytic streptococcus infection and later rheumatic fever or hemorrhagic nephritis.

4) Psychological Stress: Factors Which Operate Through Their Effect on the Central Regulating System (Brain and Mental Apparatus): All the factors so far listed are of such a nature that they may exert their influence directly at the level of cells, tissues, or organs, involving the central regulating systems only secondarily, if at all. However, if the neuroendocrine system and the mental apparatus are indeed the systems whereby the organism maintains adjustment of its internal environment in relations to the external environment, and thereby maintains growth, development and organism integrity, we must concede the possibility that a large proportion of the influences which determine health or disease are mediated in one way or another through this system. Accordingly, it is necessary to examine the extent and manner to which the predisposition for or precipitation of disease is dependent upon processes mediated through the mental apparatus and the central nervous system and to explore the patterns of disturbance which may be evoked thereby. This requires an understanding of what constitutes psychological stress. *Psychological stress refers to all processes, whether originating in the external environment or within the person, which impose a demand or requirement upon the organism, the resolution or handling of which necessitates work or activity of the mental apparatus before any other system is involved or activated.* This may be contrasted to the factors already discussed—microorganisms, physical trauma, poisons, deficiencies, etc., which effect first the operation or function of biochemical or physiological systems, sometimes including those of brain, and only involve the mental apparatus secondarily. Conceptually, for a situation or process to constitute a psychological (rather than physical) stress, it must pass not only through the systems of perception of the mental apparatus, but it must also be capable of some type of psychic representation or expression, conscious or unconscious. In other words, it must be capable of being perceived, experienced, and represented in the mind of the subject, although not necessarily *in toto* or consciously, and it must be manifest to the subject and/or observer in psychological terms. The *action* of a microorganism or a chemical substance does not satisfy these criteria, but the *idea* of an infection or a poison does. But once a microorganism or a poison has exerted its influence, the resulting bodily changes may include processes which have the capacity to penetrate the perceptual thresholds of mental apparatus. Therefore, a somatic disorder can also come to be a psychological stress. Obviously, some situations represent both at the same time. An injury, for example, will simultaneously be experienced psychologically and physically.

Highly individual factors will determine what particular situation or process will constitute a psychological stress for any particular individual. Nonetheless, experience permits us to recognize certain categories of phenomena as being the main means whereby psychologic stress may come about.

a) Loss or threat of loss of psychic objects: These are represented by persons, ideals, valued possessions, job, body function and image, social roles, goals, home, country, etc.

These refer to the variety of processes which in development exist first external to mental apparatus and psychic experience, but which subsequently come to constitute in aggregate the basis of a person's concept of himself, thereby contributing to effective ego function and to the continued and sustained sense of intactness, fulfillment, success, and hope. It is this dependence on psychic objects which renders the individual vulnerable to their loss or threat of loss and imposes the requirement for some kind of adjustment in compensation, of which grief and mourning represent the most familiar response. What constitutes the meaningful psychic objects for any individual is determined by many details of his life experience and may be ascertained only through the investigation of his life history. However, some of the universals of infant and child development determine that early family figures and early family ideals in particular will exert a major influence on the nature of later objects and modes of relating to them.

b) Threats to the body: Injury to the body, the infliction of pain, mutilation, etc. and threats thereof are a prominent source of psychological stress. In general, the human being seeks to protect himself from such dangers and he responds to psychic experiences that have this implication for him as constituting an imminent threat, requiring defense or adjustment. This will be so whether the danger is a real external one or whether it is primarily derived from intrapsychic elaboration, unconscious fantasy, persistent infantile conflict, etc. Again, what symbolically (as well as actually) constitutes such a danger is dependent upon the individual's past experience and his past successes or failures in coping therewith. Obviously, all the physical factors already considered become potential psychologic stresses when they can be conceptualized or when their effects can be experienced psychologically.

c) Frustration of drives: This category of psychological stress recognizes the built-in biological drive organizations which press for discharge either in response to developmental processes (*e.g.*, adolescence, the menstrual cycle) or upon stimulation by imagery or from the environment. A major aspect of the development of each individual has been the successive mastery by the mental apparatus of the drive apparatuses, so that satisfaction of need can take place with due regard for the requirements of reality. This developmental process carries with it the inevitability of intrapsychic conflict and of internally as well as externally imposed controls which at certain times serve to inhibit, deflect, or pervert the drive impulses. When intrapsychic conflict develops, the drive can come to constitute a psychologic stress for the individual, requiring some sort of resolution, not only in the sense that satisfaction of the drive may be conceived as somehow dangerous or undesirable, but also that the drive is not discharged and the need remains unfulfilled. Again the highly individual qualities of this situation must be underscored. When in the adult there is a persistence of a preference for certain modes of discharge or object choice more appropriate for infancy or childhood, the possibility of intrapsychic conflict and frustration of drives is much greater, predisposing to illness.

All three of these categories are obviously closely interrelated and overlap. Their division is determined mainly by the character of the initiating circumstances; *i.e.*, loss or threat of loss, injury or threat of injury, or drive frustration with or without increment, but each may in turn implicate the others. Thus a sexual or destructive impulse may have to be inhibited because it will threaten an object loss or a physical injury. Or a threat of injury or loss may stir up an intolerable degree of destructive anger or an unacceptable sexual impulse. Or a threat of injury may be psychologically experienced in terms of an object loss, meaning the loss of a valued body part or function, rather than in terms of pain and suffering. Regardless of the nature of such interrelations, all these psychological stresses are not only mutually perceived or experienced through the mental apparatus but they also have the capacity to disrupt the dynamic steady state of the mental appartus. We will now consider how this my be reflected in the subsequent function of the mental apparatus and in the rest of the body; in other words, we will deal with the direct and indirect consequences of psychological stress.

IV. PATTERNS OF RESPONSE TO PSYCHOLOGICAL STRESS AS FACTORS IN DETERMINING THE MANIFESTATIONS OF ILLNESS

Since by definition we specifiy that psychological stress involves first the mental apparatus, we can also say that the first response to a psychological stress, whether it be primary or secondary, will be psychological and/or behavioral. But there may also be simultaneous and concomitant physiological or biochemical changes in the body which in turn may permit, facilitate, or precipitate other types of somatic processes which do not directly involve the mental apparatus. Listed in this order the range and variety of responses to psychological stress are as follows:

a) An unpleasant effect, such as anxiety, anger, disgust, shame, guilt, helplessness, or hopelessness will be the first indicator of a disruption of the dynamic steady state. If the stress is brief or if ego processes succeed quickly in achieving a solution, the unpleasant affect diminishes, changes in quality, or ceases. When the defense mechanisms are not immediately available or are unsuccessful, the effects will include various quite distinctive concomitant physiological, biochemical, and behavioral changes. If the effect persists but its ideational representations are distorted, changed, or denied so that it remains unrecognizable by the subject, the concomitant bodily changes may still persist.

b) The unpleasant effects, once induced, may persist for an inappropriately long time or to an inappropriately intense degree. These may now be considered to be pathological affective states and are usually associated with manifest bodily changes, generally reversible.

c) The attempts to overcome the stress, resolve the conflict, and dissipate the unpleasant effect(s) may include inappropriate, unrealistic, or repetitively unsuccessful ego mechanisms which in various combinations and constellations make up the variety of psychopathological states known as the neuroses, psychoses, perversions, and character disorders, including patterns of abnormal behavior and conversion reactions.

d) The manifest behavior evolving under c) may directly or indirectly expose or predispose the person to other varieties of environmental stress, such as injury, poisons, drugs, dietary deficiency, etc., with all the consequences already mentioned. In other words, the inadequacies or inappropriateness of the person's attempt to deal with this intrapsychic distress may include behavior which does not properly evaluate or avoid the stresses of the external environment or renders the person incapable to do so.

e) The biochemical and physiological concomitants of sustained or intense effects may, in the susceptible individual, directly or indirectly put an already defective system under strain (*e.g.*, the effect of anxiety or rage on a damaged heart) or accelerate, precipitate, enhance or uncover preexisting, sometimes latent, pathological processes at a biochemical organ or system level (*e.g.*, an infection, neoplasia, diabetes, peptic ulceration, etc.).

f) The secondary consequences noted under d) and e) will in turn have an impact on the mental apparatus which in some cases and in some respects may compound the stress and in other cases or respects may have reparative effects. Some secondary somatic consequences may also directly affect the function or metabolism of the brain, thereby again affecting the mental apparatus (delirium).[9]

These various categories of responses to psychological stress are thus mutually inclusive and interrelated. All or any combination may occur in the same individual either at the same time or in sequence or cycles. Also, psychological stress as an etiological factor may operate as the direct or indirect route whereby other etiological factors may be brought into activity, as they in turn may achieve the quality of psychological stresses. From the developmental perspective, what was a somatic factor earlier in life may form the basis for psychological stress later by influencing the limit or variety of adjustments possible. No linear concept of etiology is appropriate, but rather the pathogenesis of disease involves a series of negative and positive feedbacks with multiple simultaneous and sequential changes potentially affecting any system of the body.

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[9] G. L. Engel and J. Romano, "Delirium, a syndrome of cerebral insufficiency," *J. Chron. Diseases*, vol. 9, p. 260; March, 1959.